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MODIFIABILITY OF MICROORGANISMS AND THE PROBLEM OF OBTAINING LIVE VACCINES

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As a result of the increase in material well-being and the culture of the population and in consequence of the development of medical science and improvement of public health protection, smallpox, cholera, plague, and recurrent fever have been eliminated in the USSR. Malaria, typhoid, typhus, and diphtheria are encountered only sporadically and in individual instances.

At present, the task is to eliminate completely a number of other diseases and to achieve a still greater decrease in the incidence of infectious diseases. The solution of this problem is feasible from the scientific point of view. All prerequisites for actually accomplishing this task exist in the USSR. It is obvious that, within the system of measures to be carried out to eliminate infectious diseases, the means of specific prophylaxis and therapy will not lose in significance. Consequently, the problem of obtaining new and highly effective bacterial preparations remains one of the most urgent to be solved by contemporary microbiology.

It is well known that vaccines prepared from live microorganisms, attenuated so fas as their virulence is concerned, are the most effective. The application of such vaccines has not been as widespread as one might expect, considering their effectiveness. At present, this method of prophylaxis is still not generally accepted.

The explanation for this state of affairs is as follows: In microbiology, particularly in the theory of the modification of microorganisms, regarded as the theoretical basis for the production and application of living vaccines, the basic and leading trend was represented by the idealistic and monomorphistic ideas implicit in Kohn's and Koch's theory of monomorphism, the theories of dissociation and cyclogeny, and Weismannism and Morganism. These concepts, which start from the principle of the immutability of species of microorganisms and of the constancy of their hereditary basis, led to the conclusion that a nonvirulent vaccine strain, by reason of the constant character of its properties, may revert to the initial, virulent state and, instead of producing immunity, produce the disease.

This assumption always constituted a deterrent to the development of live vaccines. It still is a deterrent, so far as some investigators are concerned. This is the reason the solution of the problem in regard to the application of live vaccines requires a prior solution of the problem as to whether a vaccine strain may revert to the virulent state and thus bring about the process of infection.

To answer this question and to outline the paths to be followed by further research on the development and application of live vaccines, one must take under consideration the general problem of the modifiability of microorganisms.

After the 1948 meeting of the All-Union Academy of Agricultural Sciences imeni Lenin, investigations on the problem of the modifiability of microorganisms were launched at various institutes in the USSR. These investigations are being conducted on a particularly extensive scale at the Institute of Epidemiology and Microbiology at Gor'kiy under the direction of Prof F. G. Grinbaum, at the Institute imeni Mechnikov in Moscow under the direction of V. A. Krestovnikova,

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at Prof G. P. Kalin's Laboratory by Prof S. I. Muromtsev, V. P. Kashkin, and V. P. Kosmadamianskiy, at the Institute of Experimental Medicine in Leningrad under the direction of A. A. Smorodintsev, at the Saratov Institute "Mikrob," at the Institute of Epidemiology and Microbiology imeni N. F. Gamaleya in Moscow (particularly at V. L. Troitskiy's Laboratory at that institute), at the Institute of Virology imeni Ivanovskiy, and at a number of other institutes and laboratories.

These investigations were initiated to obtain factual data which would enable us to solve the basic problem of whether the nature and substance of microorganisms change under the effect of the factors of environment or whether the micoroorganisms, as has been asserted by the protagonists of monomorphism and of autogenetic concepts, retain their hereditary substance and their inner content in a stable manner under any conditions. In connection with this basic methodological problem, problems in regard to the regularities of the formation of species and of the interspecies and intraspecies modifiability are also approached.

In contradistinction to the autogenetic concepts adhered to by some foreign investigators, it could be shown in the course of this work and asserted with certainty that the evolution of microorganisms and the modification of their hereditary characteristics and their nature are subject to the general laws applying to the evolution of plants and animals. It has been shown that, when the conditions of existence are changed, the microorganisms change their hereditary characteristics and nature.

Investigations carried out by D. G. Kudlay, N. S. Semsheva, M. G. Skavronskaya, G. N. Gadziyeva, and others have demonstrated that when microorganisms of a certain species are cultured on a nutrient medium in which the principal source of nitrogen nutrition is formed by products of decomposition or chemical complexes such as the complete antigen, nucleoproteiods, etc., derived from another, related species, substantial changes take place in the characteristics and nature of the microorganisms of the first species. Under the conditions mentioned, the first microorganism acquires all principal characteristics of the microorganism on whose products of metabolism it was cultured. For instance, B. coli, on being grown in a medium in which the source of nitrogen was formed by the products of metabolism of paratyphoid, typhoid, or dysentery microbes, acquires the biochemical, serological, antigenic, and partly the immunizing properties and characteristics of these microorganisms. Conversely, when typhoid and paratyphoid bacteria are cultured on a medium which contains, as a source of nitrogen nutrition, the products of metabolism of B. coli, these microorganisms acquire the essential characteristics of B. coli.

The fact that a thorough change in the nature of the modified variants has taken place can be seen when they are subjected to chemicoimmunological study. Investigations carried out by workers at our laboratory [Institute of Epidemiology and Microbiology imeni N. F. Gameleya, Academy of Medical Sciences USSR], Kudlay and Skavronskaya, in collaboration with the associates at the chair of biochemistry of the [Moscow] State University, Prof A. N. Belozerskiy and A. S. Spirin, applying methods of chemicoimmunological analysis, have shown that directed modification of the properties of a microorganism may involve a change in its metabolism so thorough that the microorganism can no longer be regarded as belonging to the initial species. For instance, it has been established that the alkaligenic varieties and the varieties producing fermentation artificially obtained from B. coli differ sharply from the initial culture, both so far as their chemical composition and so far as the presence of specific nucleoproteid complexes are concerned.

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One must particularly emphasize the problem pertaining to the virulence of the new forms obtained, because this problem has a direct relation to the preparation of live vaccines.

It has been shown in the investigations by Kudlay and Semcheva that B. coli, on acquiring the biochemical and serological characteristics of paratyphoid (Breslau) bacilli, brings about the death of mice on intraperitoneal with the same doses as those of the initial [paratyphoid?] culture. However, the mice cannot be infected by administering the culture perorally, while a paratyphoid culture, on being given perorally in very small doses, produces the disease and the death of the animals.

Workers at the Saratov Institute "Mikrob" who were active under the direction of N. N. Zhukov-Verezhnikov have demonstrated that the causative factor of plague under certain conditions may acquire all characteristics and properties of the causative factor of pseudotuberculosis of rodents.

Of great importance are the investigations into regularities in the modification of heredity of viruses. The work done by M. A. Morozov, L. A. Zil'ber, A. A. Smorodintsev, A. T. Kravchenko, V. M. Zhdanov, V. A. Krestovnikova, and others established that the modification of the properties of viruses is subject to the universal biological laws governing the evolution of animals and plants, just as is the modification of bacteria.

Limiting ourselves to the examples cited, we shall attempt to draw conclusions following from the multiplicity of investigations carried out and having a direct relation to the problem of obtaining live vaccines. These conclusions are as follows:

1. The substance of the microbe, its nature, and its heredity, as they originated and were formed in the process of evolution, may change when the microbe is affected by qualitatively different conditions of existence, under which it is forced to assimilate products of nutrition which do not correspond to its [original] nature. Under the circumstances, the nature of the microbe and its individual and species characteristics are changed.

2. The new species characteristics and properties acquired by the microorganism are hereditary and irreversible under the condition that the quantitative changes become qualitative modifications; in other words, when the action exerted by the conditions of the environment, i.e., the action of the transforming factor, brings about a radical change in the metabolism. In cases when nonessential characteristics of the microorganism are changed which do not affect its qualitative species characteristics, the newly acquired characteristics are lost rapidly and the microorganism reverts to its initial state.

3. The modification of the hereditary properties of microorganisms, i.e., formation of its species characteristics, proceeds gradually at first, i.e., the microorganism undergoes an evolution. After this, a sudden jump takes place. The changes which the microorganisms undergo represent the result of an "adequate" compensatory reaction of the living organism to the changed conditions of existence.

These conclusions are definitely of great importance from the standpoint of the principles involved. They enable us to give a negative answer to the question formulated earlier in regard to the reversion of vaccine strains to the initial, virulent stage. The retrogression of vaccine strains is made impossible first of all by the fact that the acquired characteristics and properties of the microorganisms are stable. The vaccine strain is not only a strain the virulence of which has been lowered, but it is also a qualitatively different strain which has a hereditarily fixed set of properties and characteristics.

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This strain is capable of inducing a qualitatively new process which is directed toward the establishment of immunity. A second reason why the retrogression of vaccine strains is impossible is that the acquisition of new properties and characteristics requires a prolonged action of the transforming factor on the microorganism. The contemporary technique of preserving vaccine strains and of preparing and applying new vaccines completely excludes the possibility that vaccine strains may revert to the initial state.

It is known that vaccine strains are preserved under strictly standardized conditions. A single application of the vaccine strain and its low viability in the body exclude the possibility that the virulence may increase. On the contrary, the long experience in the application of vaccinia, the vaccine against rabies, and the vaccine against tuberculosis gives reasons to assert that changes in the properties of vaccine strains have a greater tendency to proceed in the direction of decreased pathogenicity and an increase in the tendency to become saprophytic than in the direction of an increase in the pathogenic characteristics. This is understandable from the standpoint of evolution, because virulence, phylogenetically speaking, is a more recently acquired characteristic of the organism than its saprophytic tendencies.

However, investigations carried out at our laboratory have established that the stability of the newly acquired properties is preserved only in cases when a radical change in the principal characteristics and properties of the microorganism has taken place, particularly a change in the antigenic structure. If the characteristics have been changed only partially, regression takes place rapidly. This circumstance must be taken into consideration when vaccine strains are prepared. One cannot assume that every microorganism which has lost its virulence may be used as a vaccine strain, even if it retains its immunogenic properties.

Thus, investigations on the modification of microorganisms show convincingly that it is theoretically possible to obtain vaccine strains which have a firmly established modified inheritance and do not present any danger of reversion to the virulent state. Although we consider that the question in regard to the possibility of obtaining vaccine strains has been decided in principle, we must add that one should not draw the conclusion that it is necessary to do research on the subject of obtaining vaccine strains active against all infectious diseases. From our point of view, one must approach the solution of this question by considering the clinical characteristics of the disease, its pathogenesis, and the specific nature of the immunity against the disease. As far as infections are concerned, in which the poisoning with a toxin is a basic factor in the pathogenesis and clinical course of the disease, so that the immunity is determined principally by the antitoxic action, a search for vaccine strains is not indicated. There is no valid reason for developing vaccine strains derived from the causative factors of diphtheria, tetanus, botulism, and similar diseases when application of an antitoxin enables us to create an antitoxic immunity almost equal in strength to the immunity acquired after recovery from the disease. The production of vaccine strains is indicated only so far as those infectious diseases are concerned in which the pathogenesis is determined by septicemia or bacteriemia and the immunity bears an antibacterial character.

As far as these infections are concerned, it is advisable to develop vaccine strains even in cases when these strains do not produce a stable and lasting immunity. This should be done even in cases when a so-called nonsterile immunity, accompanied by an allergic condition, is produced. The effectiveness of inoculations against tuberculosis and brucellosis forms a sound basis for this assertion and confirms its correctness.

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What is the direction in which further research on the production and application of live vaccines should proceed?

It must be stated with regret that the answer to this question is difficult and that the problem has not been adequately studied. To answer this question, one must know in every actual case what morphological and biological properties determine the virulence of the microbe and its immunizing properties, how these properties of the microorganism have formed in the process of evolution, and whether or not they are connected with each other or may be separated from each other. To answer the question which has been set, one must also know at what time and during what period of time one must exert an action on the microbe for it to acquire the reduced virulence needed by a vaccine strain and at the same time for it to preserve its capacity to bring about immunity. All this requires extensive research on the biochemistry of microorganisms and also on the nature and characteristics of the metabolism of every individual species. Obviously, one must also investigate individual bacterial cells, because it is known that the transformation of the whole population of bacteria into a vaccine strain requires much effort and involves work which does not lead to the desired result by reason of the fact that individual cells have their own distinct characteristics [which deviate from the average].

Without a solution of the problems involved, the production of vaccine strains will always have a purely empirical and accidental character. However, although the problem is not readily soluble, one may definitely conclude from theoretical considerations that it can be solved. This is indicated by the investigations being carried out on the subject, although the results obtained are still meager. What I have in mind in saying this are the investigations on the elucidation of the biological and biochemical peculiarities and characteristics of the metabolisms of vaccine strains as compared with the initial culture.

The investigations carried out indicate, without doubt, that virulence and immunogenicity are distinct and separate qualities in the majority of microorganisms which find a distinct expression in the structure and the biological peculiarities of the bacterial cells.

Thus, according to Ginsburg's data, the vaccine strain STI differs from the initial strain in the shape of its colonies and, furthermore, in that it has lost the capacity to form capsules. All other characteristics of the microorganism remain unchanged. On subcutaneous or cutaneous application, the strain brings about local inflammation, penetrates into the blood and into the internal organ, and produces a strong and lasting immunity.

Tsuverkalov and Krasov have investigated the chemical composition of the first Tsentsovskiy vaccine and the second Tsentsovskiy vaccine as compared with B. anthracis. They have not been able to find any significant chemical differences between the vaccine strains and the virulent culture of the causative factor of anthrax. However, they note that the content of lipoids in the microorganism increases together with the increase in virulence.

The strain BCG [Bacillus Calmette-Guerin] barely differs from the virulent culture so far as its behavior in culturing and its biochemical properties are concerned. The deviation in the content of fats and lipoids is insignificant quantitatively, as Calmette has indicated. Model' found that the content of lipoids in these strains is constant, while the content of wax is higher in the pathogenic culture. However, notwithstanding the insignificant nature of the chemical changes, the BCG culture is qualitatively quite different from the initial, virulent culture.

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e vaccine strains obtained from the causative factor may differ from the initial culture in the shape of their colonies. According to the data of M. P. Pokrovskaya and a number of other investigators, the vaccine strain is of the S type, while the virulent strain is of the R type. Although the two strains do not differ from each other in biochemical properties and antigenic structure, they differ sharply as far as their pathogenicity is concerned.

According to the data of B. Ya. El'bert and T. A. Gayskiy, nonvirulent tularemia strains contain the O-antigen, are devoid of the N-antigen, and do not have allergenic properties, as distinguished from the virulent strains. So far as the remaining properties are concerned, there is no difference between the two types of strains.

It follows from the data discussed that the vaccine strains do differ from virulent cultures, but that the differences are very insignificant and that they can be detected only in the course of precise chemical and serological analysis. In this type of investigation, the fact that insignificant changes in the metabolism have taken place can be established. These changes determine the biological characteristics and particularly the virulence of the vaccine strains. Unfortunately, investigations on the subject are being conducted at present on a very limited scale. These investigations have not as yet yielded answers to the questions asked above. The formulation of a single principle and method of obtaining vaccine strains cannot be achieved without an answer to these questions.

Let us indicate the ways that should be followed by subsequent research, starting with the history of the problem, the practical experience acquired in the application of live vaccines, and the general relationships which have been discovered in the study of the modifiability of microorganisms.

The first vaccine prepared from a living microorganism was Jenner's smallpox vaccine. M. A. Morozov has demonstrated that the virus of vaccinia is the virus of smallpox, which as a result of passages through the organism of cows has lost its virulence with reference to human beings.

As a result of prolonged passages of the virus of rabies through the brains of rabbits, Pasteur obtained a live vaccine against rabies. He also deserves credit for developing a live vaccine against anthrax. By culturing the causative factor of anthrax at a temperature of 42-43°, Pasteur established that B. anthracis becomes less virulent under these conditions [after being modified]. Gerard and Robik [Robique?] obtained a vaccine strain of the causative factor of plague as a result of passing a virulent culture through agar-agar media at 16-20° for a prolonged period (5 years). Sue [Souet?] obtained a nonvirulent strain of plague by growing the culture at 41-42°.

Calmette and Guerin obtained their strain by culturing the causative factor of tuberculosis of the bovine type on potatoes combined with bile and glycerine. The process of culturing took 13 years.

These investigators were of the opinion that the nutrient medium selected by them, while changing gradually the physicochemical properties of the culture, does not modify its immunogenic properties.

Gayskiy obtained a vaccine strain of B. tularense by aging the culture. Khatenever, Mayskiy, and Yemel'yanova obtained vaccine strains of the same microorganism by culturing it on differing media and applying a different temperature [i.e., a temperature different from the optimal]. Ginsburg obtained a nonvirulent strain of the causative factor of anthrax by using the method of cultivation on such nutrient media and under such conditions that the capacity to form capsules was lost.

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Vaccine strains against plague were obtained by various methods. Pokrovskaya, Zhukov-Verezhnikov, Khvorostukhina, Korobkova, and others used the action of bacteriophage for this purpose. Otten obtained a strain of plague which spontaneously lost its virulence when the culture was kept for a period of 4 months in agar-agar.

Cotton, Box, and Smith obtained the vaccine strain Br. abortus bovis Bo 19 after culturing the initial strain for 6 years on a potato medium.

Thus, the vaccine strains available for practical use at present have been obtained by various methods and are dissimilar so far as their origin is concerned. In the majority of cases, they have been obtained as a result of exposure to unfavorable nutrient medium, deviation from the optimum temperature, action of bactericidal factors producing diverse biological, chemical, and physical effects, etc. In some cases, in order to obtain vaccine strains, the method of passing through the organism of nonreceptive animals is used or the introduction of the virulent causative factor into the tissues and organs of a definite species of animal, where they do not find favorable conditions for their propogation and existence.

Occasionally, vaccine strains form in an apparently spontaneous manner from virulent cultures when the latter are stored under laboratory conditions without being reseeded. An example is the antiplague vaccine strain obtained at the Saratov Institute "Mikrob."

Finally, unchanged microorganisms are used in the capacity of vaccine strains when these microorganisms are related genetically to another microorganism and can create a cross-immunity with reference to that microorganism as, for example, the vaccinia strain can with reference to smallpox.

Scrutiny of the methods by which vaccine strains can be obtained shows that the same factor may be used for obtaining vaccine strains from different species of microorganisms. For instance, the application of the temperature factor in combination with passages of the organism through artificial nutrient media has made possible the production of vaccine strains from the causative factors of anthrax, tularemia, plague, and tuberculosis. On the other hand, different factors applied to the same microorganism may lead to the desired result.

It is known, for instance, that vaccine strains of plague have been obtained as a result of prolonged passages, prolonged storage of the strains without reseeding, and the action of bacteriophage on the culture. A vaccine strain of anthrax was obtained by Pasteur as a result of exposing the strain to a modified temperature, while Ginsburg obtained the same result by using special nutrient media and by applying the method of selecting colonies devoid of capsules.

Thus, the methods of acting upon the microorganisms for the purpose of obtaining vaccine strains from them are not uniform. This is understandable, because the ways along which different species evolve are different. One cannot, therefore, assume that there can be a single method of obtaining vaccine strains from all microorganisms.

It follows from the preceding discussion that, in further investigations on obtaining vaccine strains, one must apply and investigate not only the methods which have already yielded positive results, but also methods which have not yet been investigated.

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This is also important for the reason that, with the aid of different methods applied to the same microorganism, one may obtain strains which have different immunizing properties. For instance, the strain STI obtained by Ginsburg proved to be more effective than the strains of Pasteur and Tsenskovskiy. In connection with this, let us consider the methods of obtaining vaccine strains which have not yielded practical results as yet, but which nevertheless seem promising from this standpoint.

So far as the application of antibiotics for the purpose in view is concerned, investigations carried out by Kh. Planel'es, V. L. Troitskiy, and their collaborators, Z. V. Yermol'yeva and her collaborators, as well as other investigators, demonstrated that microorganisms may acquire new and heriditarily fixed characteristics and properties as the result of the action of antibiotics on them. Specifically, they acquire a resistance to the action of antibiotics, and their virulence and immunogenic properties also change.

From this standpoint, the investigation of antibiotics for the purpose of obtaining vaccine strains has received attention during recent years. Encouraging results have been obtained by A. I. Togunova, who used antibiotics to obtain vaccine strains from the causative factor of tuberculosis. V. G. Petrovskaya, by studying the action of different antibiotics (synthomycin, streptomycin, and mitserin [sic] demonstrated that one may obtain under the action of mitserin certain cultures of the positive factor of typhoid immunogenic strains which have a sharply lowered virulence.

The data cited concern the correctness of the assumption that it is necessary to study and investigate the possibility of obtaining vaccine strains with the aid of antibiotics.

In determining the ways which further research on new methods for obtaining vaccine strains must take, we should particularly stress the necessity of investigating the so-called atypical and nonvirulent strains isolated from the organism of sick persons or from objects within the environment, as well as the possibility of discovering vaccine strains among microorganisms genetically related to the causative factor of the disease.

The necessity of carrying out these investigations follows from the considerations outlined below:

It is known that the evolution of microorganisms and the formation of their specific properties and characteristics take place under definite multiple conditions of interaction with the factors of the environment and other conditions pertaining to their existence in nature. It is difficult to assume that the evolution of microorganisms took place in one direction only, namely the direction leading to the formation of pathogenic species. It is evident that microorganisms which have the properties of vaccine strains also arise in nature and that the development of these strains presumably takes place much more effectively there than under experimental conditions. The problem consists in finding ways and means of discovering these forms. We understand the complexity and difficulty of the investigations involved. However, this line of investigation should not be neglected so long as we do not know the way which will lead with certainty to the results desired by us.

The idea that it is advisable to search for vaccine strains among microorganisms related to the pathogenic factor is confirmed by the well-known facts that the vaccinia virus can be used for the prophylaxis of human smallpox and that the bovine strain Br. abortis bovis No 19 can be used for immunization against brucellosis.

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Of particular importance are investigations aiming at the development of vaccine strains derived from the causative factors of encephalitides and rickettsioses. Investigations along this line are definitely promising.

Work carried out by A. T. Kravchenko and his collaborators indicated the possibilities of bringing about a lasting change in the biological properties of viruses when they are cultured in tumor tissues. According to the experimental results of Kravchenko and Yakovlev, it is possible to obtain in this manner a strain of the tick encephalitis virus which has a sharply lowered virulence toward white mice and possesses immunogenic properties. Strains of this type have not yet been applied practically. However, the principle of obtaining vaccine strains by culturing viruses under unusual conditions of existence in various organisms and tissues of animals is not without importance from our standpoint.

In the search for new methods of developing vaccine strains from viruses, the investigations conducted by L. A. Zil'ber, A. A. Smorodintsev, V. M. Zhdanov, M. I. Sokolov, V. D. Solov'yev, and others are of undoubted importance so far as the possibility of obtaining vaccine strains for the prophylaxis of influenza is concerned.

The investigators who carried out this research are of the opinion that in order to produce vaccine strains of influenza, adaptation of the microbes [sic] to the tissues and organs of the human body is necessary, because the strains of virus adapted to the lung tissue of mice do not possess immunogenic properties. From this standpoint, the suggestion of Smorodintsev in regard to the necessity of searching for vaccine strains by isolating them directly from the organism of patients suffering from influenza deserves attention.

Starting from the data obtained in our investigations, the results of work on the directed modification of microorganisms of the intestinal-typhoid group and analogous investigations carried out by G. P. Kalina and his collaborators, and the data obtained in the work done by Griffiths, Avery, McLeod, and others on the transformation of pneumococci, one may conclude that this method of obtaining vaccine strains is definitely of importance.

Further investigations along these lines should be conducted by culturing microorganisms on media which contain definite chemical complexes, particularly those complexes which determine the immunizing properties of the microorganism. In doing this, one must apply the method of selection, because modification of the inherited properties of all individuals of the bacterial population requires much time and effort.

Work on the filterable forms of microorganisms is closely connected with the problem of the modifiability of microorganisms and the development of live vaccines. Without expatiating on this problem as a whole, let us touch on those aspects of it which bear on the development and application of live vaccines.

At present, the fact that filterable forms of microorganisms exist has been definitely proved by the work of Suknev and his collaborators, and the investigations of Kalina, Krestovnikova, and a number of other scientists. However, the question in regard to the nature of these forms and their significance in pathology, immunity, and epidemiology has not yet been solved or clarified.

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The investigation of biological properties of regenerated forms obtained from the filtrates of cultures of bacteria indicates that practically all of the filterable forms are devoid of virulence. At the same time, work done by Suknev, our work carried out from 1934 to 1936, as well as investigations by Kalina, Krestovnikova, Kagen and Koptelova, Il'yashenko, Omel'chenko, and Miterova, show with certainty that the immunogenic properties of regenerated cultures are considerably lower than those of the initial cultures, even when the regenerated forms are applied in the living state for purposes of immunization.

In subjecting to study the filterable forms with a view toward obtaining vaccine strains from them, one should take into consideration only one property of the filterable forms, namely the great lability of their characteristics. The fact that the filterable forms have this property gives reason to believe that they may form the plastic material from which it will be possible, by applying the methods of directed modification, to obtain the needed species and forms of microorganisms that will be suitable for practical purposes. However, this is purely speculative at this stage. Further research on the nature of filterable forms will either prove or disprove the correctness of this assumption.

While recognizing the necessity of conducting work on the development of live vaccines and the promising nature of this work, we must not neglect the perfection of existing vaccines from killed bacteria and the development of new and more effective vaccines derived from such microorganisms or the products of their vital activity.

Particular attention should be given to the investigation of immunizing chemical complexes isolated from bacterial cells. The significance of work along these lines is determined by the fact that chemical complexes having strong immunogenic properties can be introduced into the organism without ballast substances and in an extremely small quantity and volume. These circumstances give reason to believe that such vaccines may be no less effective than vaccines derived from live microorganisms. The necessity of conducting research on this subject becomes evident if we consider that, with reference to a number of infections, the method of obtaining live vaccines does not offer much promise.

In summarizing the discussion of the methods of obtaining live vaccines and the lines along which further research on this subject should be conducted, one may say that these methods should not be the same when applied to different microorganisms. In each individual case, it is necessary to investigate and acquire a knowledge of all peculiar traits of the evolution of the microorganisms and of all regularities pertaining to tis modifiability and the nature of its metabolism. Only when these conditions are fulfilled will it be possible to obtain regularly and in a purposeful manner the desired forms of microorganisms, including vaccine strains. This work is certainly very extensive and difficult. As the same time, there is a definite promise of success, and the work is absolutely essential from the standpoint of the elimination of infectious diseases and/or a sharp reduction in their incidence.

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